

# Cardiovascular Health Study Proposal

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## Proposal Description

### Introduction [Rationale and background]:

(Subclinical) Thyroid disease has been associated with osteoporosis and fractures. Thyroid hormone has effects on osteoclasts and osteoblasts. Excess thyroid hormone leads to bone loss, clinically resulting in osteoporosis and increased fracture risk [4]. TSH may also have direct effects on bone skeleton and metabolism and thus bone remodeling by directly or indirectly acting on osteoclast and osteoblast activity [5, 6]. Subclinical hyperthyroidism (SHyper) is characterized by low TSH and normal to high-normal FT4 levels, which could explain loss of bone mineral density (BMD) and increased fracture risk. Conversely, direct effects of TSH on bone turnover with subsequent change of bone quality might account for adverse bone outcomes in subclinical hypothyroidism (SHypo).

**SHyper & skeleton:** Overt hyperthyroidism is an important risk factor for osteoporosis and fractures [7-9]. The association of SHyper and bone loss or fracture risk is however still controversial. The to-date largest prospective cohort study of 3567 adults aged 65 years or older showed over a follow up period of 13 years an increased risk for hip fractures in men with endogenous SHyper, with a non-significant trend in postmenopausal women [10]. Recently, a prospective cohort study of 1526 ambulatory men aged 65 years or older found a statistically significant association between lower TSH levels and the risk of hip fractures (HR 1.31 per SD decrease) but not for non-spine fractures [11]. A large retrospective population-based study of adult men and women found an increased osteoporotic fracture risk (hip, lower back, forearm, femur, any pathologic fracture in osteoporosis) (HR 1.25, 95%CI 1.04–1.50) in patients with SHyper [12], however after excluding patients developing overt hyperthyroidism or reverting to euthyroidism during follow-up this difference was not seen anymore. Epidemiological data on BMD in SHyper is scarce. Small cross-sectional studies in pre-menopausal women with SHyper found no reduction of BMD [13] or a small decrease [14], while studies in post-menopausal women generally showed decreased BMD [13-15]. In a prospective cohort of 361 women enrolled in a calcium trial, 10 participants overtreated with LT4 and low TSH levels (exogenous SHyper) lost spine BMD more rapidly over a follow up of 2 years than participants without known thyroid disease [16].

**SHypo & skeleton:** Overt hypothyroidism has been reported to decrease bone turnover with subsequent increase of cortical thickness but not trabecular bone [17]. However, evidence on the association of SHypo or its treatment with bone mineral density and fractures is limited. A prospective cohort of 3567 elderly adults found an increased risk of hip fractures in men with SHypo even with mild thyroid dysfunction (TSH < 10mIU/l), while no association was found for women [10]. A recent cohort of 1526 ambulatory men found no significant association of TSH or free T4 with bone loss over a follow up of 4.6 years [11]. Cross-sectional data show decreased bone turnover and conflicting evidence on the association of BMD and bone loss. In a study of men and postmenopausal women, TSH within the normal range was not associated with BMD [18], while another study found a reduced femoral neck BMD in women with SHypo [19].

At this point, 12 cohorts with incident fracture data, including 4 cohorts with BMD data, have joined the Thyroid Studies Collaboration, resulting in sufficient statistical power to thoroughly assess the association between all known TSH levels and fracture risk or BMD in over 50'000 individuals.

**Research Hypothesis** Is subclinical thyroid dysfunction (SHyper, SHypo) associated with increased subsequent fracture risk (hip, non-spine, spine, all combined)? Is subclinical thyroid dysfunction (SHyper,

SHypo) associated with a greater bone loss as assessed by serial measurements of hip and spine BMD? Are TSH levels within the normal range and/or thyroxine therapy associated with increased fracture risk (hip, non-spine, spine, all combined) and/or lower BMD? Is fracture risk in subclinical thyroid dysfunction mediated by its effects on BMD? Data [Variables to be used, sample inclusions/exclusions]:

Inclusion criteria: All individuals with known baseline serum TSH and free T4 that do not fulfill the criteria for overt hyperthyroidism or overt hypothyroidism.

Exclusion criteria (for all cohorts): Missing data on TSH.

Variables (if available)

Demographics and baseline variables: Age at menopause, Alcohol use, History of falls, History of fractures, History of osteoporosis Baseline medication: Anti-osteoporosis medication (bisphosphonates, SERMs, parathyroid hormone, calcitonin), Oral corticosteroids, Oral estrogens, Anti-thyroid medication, Lithium, Thiazides, Anti-diabetic drugs (oral, insulin) Fracture events: Location of fracture (specific site), Fracture mechanism (pathologic, stress, regular), Objective confirmation (radiographic, surgical report, hospital discharge, other clinical report), Adjudication (ascertainment of fracture), Date of fracture BMD (baseline and follow-up): Units (g/cm<sup>2</sup>) and t-score, Measurement type (e.g. DXA), Measurement sites (e.g. hip, spine), Date of follow-up BMD measurement, Device used Follow-up TSH and FT4 measurements (Year 5)

The following data have already been provided for previous analyses:

TSH, Free T4, TPO-antibody (TPOAb), Thyroid assay information, Sex, Age, Ethnicity, Educational level, Income, Smoking status, Height, Weight, Thyroid disease, Diabetes, Levothyroxine, amiodarone, Thyroid medication use at baseline, Date of start of follow-up/thyroid function measurement Brief analysis plan and methods:

Identification of Studies: We will use prospective cohorts from our previous analyses [1, 3], identified through a systematic literature search of any language articles published from 1950 to 2011 in MEDLINE and EMBASE. To maximize the quality and comparability of the studies in the present pooled analysis, we formulated a priori general inclusion criteria. We included only full-text published longitudinal cohort studies that a) measured thyroid function with both TSH and T4, and b) assessed incident fracture events. In addition, we will update our systematic literature search of any language articles published from 1950 to 2013 in MEDLINE and EMBASE, including fractures as outcome, and invite all qualifying prospective cohorts to join the Thyroid Studies Collaboration.

Definition of thyroid function: Similar to our previous analyses [1, 3], we will use a uniform TSH cutoff level, based on an expert consensus meeting of our Thyroid Studies Collaboration (International Thyroid Conference, Paris, 2010), expert reviews [20, 21] and a previous CHS paper [22]. Euthyroidism will be defined as a TSH 0.45-4.49 mIU/L, subclinical hypothyroidism as a TSH level between 4.50-19.99 mIU/L with fT4 levels in normal range, and subclinical hyperthyroidism as a TSH level < 0.45 mIU/L with fT4 levels in normal range.

Statistical analyses: The relation between a high TSH (>4.5 mIU/L) and a low TSH (<0.45 mIU/L) versus fractures and BMD will be analyzed using Cox regression analyses. Euthyroid participants, as indicated with a serum TSH 0.45-4.5 mIU/L and a FT4 within the reference range will be used as controls. In addition, a dose-response effect will be analyzed using stratified categories for TSH as has been published before [1, 3]. For elevated TSH: 4.5-6.9 mIU/L (mild elevation), 7.0-9.9 mIU/L (moderate elevation) and 10.0-19.9 mIU/L (marked elevation) and >20 mIU/L; For suppressed TSH: 0.10-0.44 mIU/L (moderately suppressed TSH) and TSH < 0.10 mIU/L (fully suppressed TSH). An individual patient data meta-analysis will be conducted using a two-step approach, as has been done in all manuscripts so far by the Thyroid Studies Collaboration. First, we will calculate within each cohort the hazard ratios for the primary outcomes by stratified categories and continuous ranges of TSH with a Cox regression analysis using independent patient data. Two multivariate models will be conducted:

one adjusting for age, gender and BMI, and the other adjusting for age, gender, BMI, smoking status, race, menopause status, alcohol use, history of fractures, history of osteoporosis. We will further add baseline BMD to the multivariate models to assess attenuation of a relationship between TSH and fractures. As a second step, we will pool estimates across cohorts for each outcome using random-effects meta-analyses according to DerSimonian & Laird [23]. To assess the heterogeneity across studies we will use the tau<sup>2</sup> statistic, as several large studies will be included. For the data from cohorts using first generations TSH assays, we will perform a sensitivity analysis excluding these studies. Analyses will be conducted using Stata. The analyses will be performed at the Clinical Trials Unit and the University Hospital in Bern, Switzerland. Confidentiality will be kept, and none of the cohort data will be shared or used for other purposes beyond this proposal.

Sensitivity analyses will be performed excluding subjects with previous fractures or known osteoporosis at baseline, and excluding participants with levothyroxine use or under anti-osteoporotic treatment at baseline and during follow-up (when data are available), and restricting analysis to participants with persistent thyroid function, as determined by follow-up TSH and FT4 measurements (where available).

Analyses will be stratified by gender, by age under/over 75 years, by follow-up time since baseline TSH measurement (under/over 5 years), and by thyroxin use at baseline (yes/no), to assess if subclinical hyperthyroidism on thyroxin use is a risk factor for fracture.

#### Summary/conclusion:

Subclinical thyroid dysfunction (subclinical hypothyroidism and subclinical hyperthyroidism) is common, particularly in older adults. Current evidence from cross-section and few prospective studies suggests an association between subclinical thyroid dysfunction and adverse bone outcomes, such as fractures and decrease of bone mineral density, but existing data is inconsistent and conflicting. This multicenter and international proposal provides a unique opportunity to investigate such an association. A pooled analysis of large cohort studies with individual participant data is an optimal approach to address this question and to clarify the current conflicting data.

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